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Marked Improvement in Survival among Adult Croatian AIDS Patients after the Introduction of Highly Active Antiretroviral Treatment

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A B S T R A C T

We compared the survival of patients following the first AIDS event in Croatia from the period 1986–1996 to the period 1997–2000. A total of 72 (81.8%) out of 88 patients from 1986–1996 and 18 (32.1%) out of 56 from 1997–2000 died. Survival following the first AIDS-defining illness markedly improved in the period 1997–2000 compared to the period 1986–1996 (adjusted Hazard Ratio (HR) for patients surviving more than 6 months: 0.11, 95% confidence interval (95% CI)=0.04–0.29). A CD4$^+$ cell count of $<100 \times 10^6$/L was an independent risk factor for patients surviving up to 2 years (adjusted HR=1.96, 95% CI=1.1–3.43, p=0.02). Patients with tuberculosis or fungal infections had a longer survival when compared to other diagnosis (adjusted HR=0.53, 95% CI=0.32–0.90, p=0.01). However, despite dramatic survival benefit of combination antiretroviral therapy, mortality at six months following the first AIDS event was similar in the two study periods and the one-year probability of death was still substantial (27.2%) in the period 1997–2000.

***Key words**: AIDS, survival, protease inhibitors, HAART, Croatia*

Introduction

Croatia is a South-Eastern European upper middle income country with a low level HIV-epidemic[1]. Up to December 2000, 174 cases of AIDS had been reported, most (46%) were diagnosed among men who have sex with men. Highly active antiretroviral treatment (HAART) has been provided universally and free of charge in Croatia through the national health care system since April 1998. Studies in developed countries have demonstrated striking benefits from HAART in terms of survival[2–9]. However, there are fewer reports from developing countries and none from South-Eastern European countries[10].

Croatia has a centralized system of care for HIV/AIDS and all patients are treated at University Hospital of Infectious Diseases (UHID) in Zagreb. The aim of this study was to compare the survival of Croatian patients after AIDS diagnosis in the pre-HAART era (1986–1996) to the early HAART era (1997–2000).

Subjects and Methods

In this study, data were collected retrospectively up to 1998 and prospectively thereafter. Included were patients over 15 years of age in whom the first AIDS-defining event was diagnosed at UHID. The 1993 European AIDS case definition (CDC category C) was used[11] as the inclusion criterion. Variables included as determinants of mortality were: age at AIDS diagnosis, sex, transmission category, initial AIDS defining illness, CD4$^+$ cell count, *Pneumocystis jiroveci* pneumonia (PCP) prophylaxis, antiretroviral therapy, and era of diagnosis (pre- HAART 1986–1996; early HAART 1997–2000). Each patient was considered as a censored observation at the time of last contact if lost to follow-up or known to be alive on December 31, 2002. To ensure the accuracy of the date of death, we compared our records with official mortality statistics obtained from the Croatian Public Health Institute.

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Survival times were calculated using the Kaplan-Meier method. Cox's proportional hazards model was used to examine factors associated with survival on bivariate and multivariate analysis. We included in the multivariate model predictors of survival with $p<0.20$ on bivariate comparison. Log-log plots and Schoenfeld residuals were used to check the validity of the proportional hazards assumption. Because the categories of $CD4^+$ cell count and era of diagnosis violated this assumption different survival periods were modeled for these variables according to the log-minus-log survival plot. We assumed that the hazard changed at 6 months for the era of diagnosis and at 24 months for the $CD4^+$ cell count. PCP prophylaxis was also time dependently modeled as was the type of antiretroviral treatment (monotherapy, double therapy and HAART). Both were modeled in an intention to treat fashion by fitting a 0/1 variable which coded 1 when the patient had started the drug. No adjustments were made for stopping or changing antiretroviral treatment or PCP prophylaxis. Because the variables era of diagnosis and type of antiretroviral treatment were correlated we constructed separate models for each of them. Statistical tests were conducted using SAS software version 8.2 (SAS Institute, Inc., Cary, North Carolina, USA).

Results

The population included 144 (82.8%) out of 174 AIDS patients registered in Croatian´s National HIV/AIDS Registry in the period 1986–2000. Of these, 88 (61.1%) were treated in the pre-HAART era and 56 in the early HAART era. The main characteristics of the patients are presented in Table 1. 17 (19.3%) patients from the period 1986–1996 and 48 (85.7%) from the period 1997– 2000 received HAART. The median time of initiation of HAART following the first AIDS event was 134 days (interquartile range: 66 to 359 days) for all patients and for patients in the HAART era it was 100.5 days (interquartile range: 54.5 to 210.5 days). Altogether, 90 (62.5%) patients died; 72 (81.8%) from the pre-HAART era and 18 (32.1%) from the HAART era. The one-, three- and five-year survival probabilities in the pre- HAART era were 52.1%, 22.5% and 15.4% whereas in the HAART era they were 72.8%, 68.4% and 61.9% respectively (Kaplan-Meier method). Patients treated in the HAART era had more frequently a lower $CD4^+$ cell count (below 100×10^6/L $CD4^+$ cells) compared to patients in the pre-HAART era (72% versus 36.4%, $p< 0.001$) (Table 1). Seven patients started antiretroviral monotherapy prior to AIDS, 5 of whom where from the 1986–1996 period. Only one patient started double antiretroviral therapy, and none started HAART prior to AIDS. The median age at AIDS diagnosis was 37.8 years (range: 15.9 to 65.5 years) and 39.7 years (range: 23.1 to 73.5 years) in the pre-HAART and early HAART era respectively. The median survival for patients treated in the period 1986–1996 was 13.7 months, whereas it was not reached for patients treated in the period 1997–2000 (Figure 1).

Predictors of longer survival using bivariate analysis were: era, antiretroviral treatment, type of presenting AIDS-defining illness, and PCP prophylaxis (Table 2). The hazard of death up to 6 months after AIDS diagnosis was similar in the two eras; however, afterwards it was markedly reduced for patients treated in the early HAART era, 1997–2000 (Table 2).

In multivariate analyses, survival was markedly increased for patients who received HAART (Table 2). A $CD4^+$ cell count of $<100 \times 10^6$/L was an independent risk factor for death for patients surviving up to 2 years. Patients with tuberculosis/fungal infections had better survival when compared to other diagnoses, and PCP prophylaxis did not reach significance in predicting survival difference (Table 2). When the era was included in the multivariate model, and the type of antiretroviral ther-

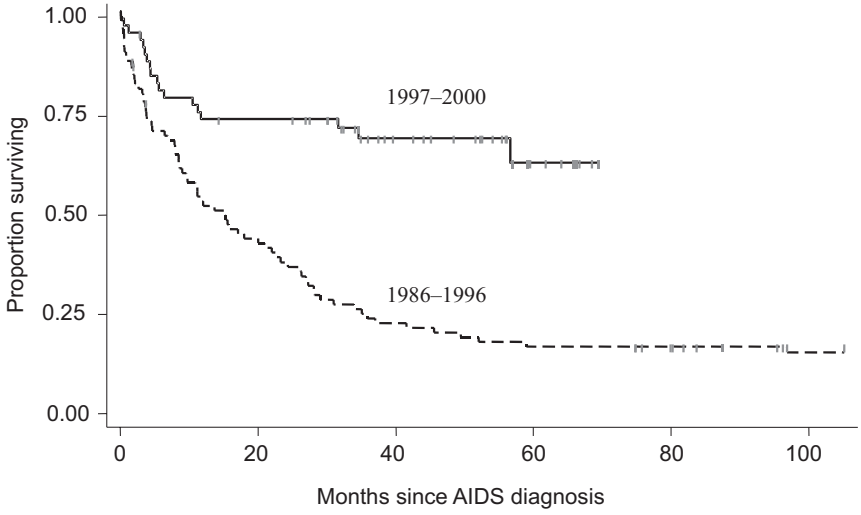

Fig. 1. The Kaplan-Meier product-limit estimates of the probability of survival after AIDS diagnosis in periods 1986–1996 and 1997–2000. Ticks indicate censored observations.

TABLE 1
CHARACTERISTICS OF THE ADULT CROATIAN AIDS PATIENTS DIAGNOSED IN THE PERIOD 1986–1996 AND 1997–2000

Patients characteristics	Time of diagnosis		Total (N=144) n (%)	p
	1986–1996 (N=88) n (%)	1997–2000 (N=56) n (%)		
Age at diagnosis				
15–39	47 (53.4)	26 (46.4)	73 (50.7)	0.495
≥40	41 (46.6)	30 (53.6)	71 (49.3)	
Gender				
Male	73 (82.9)	49 (87.5)	122 (84.7)	0.635
Female	15 (17.1)	7 (12.5)	22 (15.3)	
Exposure category				
Heterosexual	33 (37.7)	28 (50)	61 (42.4)	0.277[a]
MSM/bisexual	42 (47.7)	23 (41.1)	65 (45.1)	
IVDU	8 (9.1)	4 (7.1)	12 (8.3)	
Blood/blood products	5 (5.7)	0 (0.0)	5 (3.5)	
Unknown	0 (0.0)	1 (1.8)	1 (0.7)	
Presenting diagnosis[b]				
Tuberculosis (pulmonary/extrapulmonary)	20 (22.7)	10 (17.9)	30 (20.8)	0.534[c]
Pneumocystis jiroveci pneumonia	17 (19.3)	8 (14.3)	25 (17.4)	
Cryptococcal meningitis	8 (9.1)	8 (14.3)	16 (11.1)	
Oesophageal candidiasis	11 (12.5)	11 (19.6)	22 (15.3)	
HIV encephalopathy	10 (11.4)	4 (7.1)	14 (9.7)	
Kaposi sarcoma	9 (10.2)	3 (5.4)	12 (8.3)	
Other	24 (27.3)	20 (35.7)	44 (30.6)	
Multiple	13 (14.8)	10 (17.9)	23 (16.0)	
Concomitant HIV and AIDS diagnosis[d]				
Yes	55 (64.0)	28 (50.0)	83 (58.5)	0.118
No	31 (36.0)	28 (50.0)	59 (41.5)	
$CD4^+$ cell count ($\times 10^6$/L)[e]				
<100	28 (36.4)	40 (72.7)	68 (51.5)	<0.001
≥100	49 (63.6)	15 (27,3)	64 (48.5)	
Pneumocystis jiroveci pneumonia prophylaxis				
Yes	43 (48.9)	54 (96.4)	97 (67.4)	<0.001
Never used	45 (51.1)	2 (3.6)	47 (32.6)	
Initial treatment[f]				
No treatment	47 (64.4)	21 (40.4)	68 (54.4)	<0.001[g]
Monotherapy	17 (23.3)	2 (3.8)	19 (15.2)	
Double ART	7 (9.6)	8 (15.4)	15 (12.0)	
HAART	2 (2.7)	21 (40.4)	23 (18.4)	
Antiretroviral treatment (ever)[h]				
No treatment	39 (44.3)	5 (8.9)	44 (30,6)	<0.001[g]
Monotherapy	34 (38.6)	4 (7.1)	38 (26.4)	
Dual ART	21 (23.9)	8 (14.3)	29 (20.1)	
HAART	17 (19.3)	48 (85.7)	65 (45.1)	

[a] Comparison of heterosexual vs MSM/bisexual
[b] Total >144 because some patients had multiple presenting illnesses
[c] Comparison of cases of tuberculosis
[d] N=142 because the date of diagnosis of HIV infection was not known for 2 patients
[e] N=132 because of missing data
[f] Type of treatment given within three months after AIDS diagnosis. N=125 because patients who died within one month of AIDS and those receiving treatment before AIDS diagnosis were excluded.
[g] Comparison of HAART
[h] Total >144 because patients moved from categories
HAART – highly active antiretroviral treatment, ART – antiretroviral treatment, MSM – men who have sex with men

TABLE 2
PREDICTORS OF SURVIVAL ON BIVARIATE AND MULTIVARIATE COX PROPORTIONAL HAZARD ANALYSIS

Predictors[a]	Bivariate (N=144)[b]			Multivariate (N=120)[c]		
	Hazard ratio	95% CI	p	Hazard ratio	95% CI	p
Gender (male versus female)	1.48	0.80–2.73	0.20			
Age (< 40 versus ≥ 40)	0.81	0.54–1.23	0.33			
Exposure category (MSM/bisexual versus other)	1.14	0.75–1.72	0.54			
Concomitant HIV and AIDS diagnosis (yes versus no)	1.01	0.67–1.54	0.96			
Antiretroviral therapy						
Monotherapy	1.36	0.81–2.26	0.24	2.01	1.04–3.92	0.04
Double therapy	0.50	0.27–0.95	0.03	0.72	0.36–1.42	0.34
HAART	0.19	0.10–0.38	<0.001	0.31	0.13–0.72	0.006
Year of diagnosis (1997–2000 versus 1986–1996)						
Survival times: 0–5 months	0.59	0.29–1.19	0.14			
≥ 6 months	0.15	0.07–0.32	<0.001			
$CD4^+$ cell counts ($<100 \times 10^6$/L versus $\geq 100 \times 10^6$/L)						
Survival times: 0–23 months	1.20	0.73–2.04	0.45	1.96	1.12–3.43	0.02
≥ 24 months	0.43	0.15–1.20	0.11	0.70	0.22–2.27	0.56
Presenting diagnosis (tuberculosis/fungal[d] versus other)	0.46	0.29–0.73	0.001	0.53	0.32–0.90	0.01
Multiple initial presenting illnesses (yes versus no)	0.96	0.52–1.76	0.89			
PCP prophylaxis (yes versus no)	0.39	0.24–0.63	0.001	0.50	0.25–1.00	0.05

[a] The reference category is the second one in parenthesis.
[b] Some categories have <144 patients because there were missing data on the $CD4^+$ cell count and because patients who started antiretroviral treatment or *P. jiroveci* prophylaxis before AIDS were excluded.
[c] Patients who started antiretroviral treatment or *P. jiroveci* prophylaxis before AIDS were excluded as were those with missing data on $CD4^+$ cell counts.
[d] Oesophageal candidiasis and cryptococcal meningitis.
MSM – men who have sex with men, HAART – highly active antiretroviral treatment, CI – confidence interval

apy excluded, the survival after 6 months was markedly improved for patients in the early HAART era (Hazard Ratio, (HR) = 0.11, 95% confidence interval (CI) = 0.04–0.29, p<0.0001) compared to the pre-HAART era. Survival at 6 months was similar in the pre-HAART and HAART era (HR=0.68, 95% CI=0.3–1.52, p=0.34) in this model and other predictors did not change significantly compared to the model that included antiretroviral treatment.

The initial HAART regimen used was a non-boosted indinavir combination in 38 (58.5%) patients, a low-dose ritonavir boosted indinavir combination in 13 (20.0%) patients, and 10 (15.4%) patients started with a non-nucleoside analogue plus indinavir combination. Two patients started with a full dose ritonavir regimen and one with a nelfinavir, and efavirenz based combination.

Discussion

Survival after the first AIDS event has markedly improved after introduction of HAART in Croatia. However, during the first six months after AIDS diagnosis, survival was similar for the pre-HAART era (1986–1996) and early HAART era (1997–2000). In addition, the one–year probability of death after AIDS was still high in the early HAART era (27.2%), suggesting that improvements in the treatment of opportunistic infections are still needed. Since our patients started HAART relatively late after AIDS diagnosis, earlier administration of HAART might have improved survival. Those who died in the early HAART era presented most frequently with multiple opportunistic infections (22.2%) and progressive multifocal leukoencephalopathy (16.7%). The effect of $CD4^+$ cell count at the time of AIDS diagnosis, on survival is anticipated to be less pronounced over time; however, it was still significantly associated with survival at 2 years after AIDS diagnosis in our patient population. Similarly to patients from the pre HAART era[12] the type of AIDS -presenting illness was a significant predictor of survival. Studies conducted prior to the introduction of HAART from both industrialized and de- veloping countries have shown an association between specific opportunistic diseases and survival[13,15–18]. Patients with lymphoma and progressive multifocal leukoencephalopathy had shorter survival, conversely to those having extrapulmonary tuberculosis and Kaposi's sarcoma[13,14,16,17].

The improvement in survival observed in our study is similar to that reported from many developed countries since 1995. At 36 months, 67% of United States[9] and 58% of AIDS patients from Brazil[10] diagnosed in 1996 were alive, compared to 68.4% of our patients diagnosed in the period 1997–2000. The probability of three-year survival

from the time when $CD4^+$ lymphocyte count falls to $<200 \times 10^6$/L in different European countries ranged from 78–88%[19]. We were also able to evaluate the effect of specific antiretroviral treatment regiments comparing the use of monotherapy, double combination, and triple combination therapies. The relative hazard found in our study (HR=0.31) was similar to that from larger studies from the United States (HR=0.36)[9] and Italy (HR=0.36)[8].

Our study findings are limited by the small number of patients studied; some predictors like PCP prophylaxis, age or gender might have been significant in a larger sample. To assess the effect of AIDS-defining illnesses we had to combine many different opportunistic diseases and we were able to stratify our patients into only two $CD4^+$ cell strata. Since the period of study was relatively large, improvements in the treatment of opportunistic disease might have occurred and influenced survival.

Despite the limitations of our sample size, we studied a well-defined population at one center and obtained findings similar to larger cohorts. As expected, combination therapy with a protease inhibitor markedly improved survival in AIDS patients in Croatia. However, the occurrence of opportunistic diseases can be largely prevented by earlier diagnosis and treatment of HIV infection, and prophylaxis against opportunistic infections. Unfortunately, there are still patients who are diagnosed with HIV infection at an advanced stage of HIV disease. Currently, in Croatia around 30% of all newly diagnosed HIV-positive patients present with an AIDS- defining event. Better public information, patient education, wider screening of high-risk populations, and improved outreach to risk groups could lead to earlier HIV diagnosis and thus significantly avoiding the morbidity and mortality associated with AIDS- defining diseases.

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IZRAZITO POBOLJŠANJE PREŽIVLJAVANJA U ODRASLIH BOLESNIKA IZ HRVATSKE OBOLJELIH OD AIDS-A NAKON UVOĐENJA VRLO DJELOTVORNOG ANTIRETROVIRUSNOG LIJEČENJA

SAŽETAK

Usporedili smo preživljavanje bolesnika nakon dijagnoze AIDS-a u Hrvatskoj u razdoblju 1986–1996. g. s razdobljem 1997– 2000. g. 72 (81,8%) od 88 bolesnika iz 1986–1996. g. i 18 (32,1%) od 56 iz 1997–2000. g. je umrlo. Preživljavanje nakon prve AIDS-definirajuće bolesti se značajno poboljšalo u razdoblju 1997–2000 u odnosu na razdoblje 1986–1996 (prilagođeni omjer hazarda (HR) za bolesnike koji su preživjeli više od 6 mjeseci: 0,11, 95% CI: 0,04–0,29). Broj $CD4^+$ limfocita $< 100 \times 10^6$/L je također bio neovisni čimbenik preživljavanja za bolesnike koji su preživjeli 2 godine (prilagođeni HR=1,96, 95%CI=1,1–3,43, p=0,02). Bolesnici s tuberkulozom ili gljivičnom infekcijom imali su bolje preživljavanje u usporedbi s drugim dijagnozama (prilagođeni HR=0,53, 95%CI=0,32–0,90, p=0,01). Međutim, usprkos izrazito boljem preživljavanju zbog kombinirane antiretrovirusne terapije, smrtnost 6 mjeseci od AIDS-a je bila slična u oba razdoblja, a smrtnost nakon jedne godine od AIDS-a je bila još uvijek značajna (27,2%) u razdoblju 1997–2000.